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November 16, 2006

Dr. M. Granger Morgan, Chair
EPA Science Advisory Board, US EPA
1200 Pennsylvania Avenue, NW
Washington, DC 20460

Re: Arsenic Review Panel (9/15/06) assessment of cancer risk of inorganic arsenic

Dear Dr. Morgan,

I appreciate the intense work that the Arsenic Research Panel has undertaken in order to respond to the questions asked by EPA. I also appreciate having had the opportunity to participate in the meeting and teleconferences and to submit in writing various analyses as appropriate to their requests.

I am providing comments on the draft ARP report to identify significant deficiencies that have a critical impact on interpretation of and conclusions about the cancer risk of inorganic arsenic.

My concerns, each of which is discussed further, include that the Panel report –

(1) ignores, without even citation, studies that have demonstrated marked confounding in the Southwest Taiwan data,

(2) has given no attention to the strengths of the US 133-county study and its exposure assessment, and

(3) gives little weight to the studies that find no effect at low-dose exposures without a presentation of their study design and findings, and the meta-analyses that have integrated study data on risks from low-dose exposures.

The report states (page 36-37) that "If iAs is essential or hormetic for humans and/.or if epidemiological data could be strengthened at the low-dose range to demonstrate either a low-dose benefit or no effect at low dose, then a threshold is certain. However, at this time, while the mechanistic studies suggest that there should be a threshold, the epidemiological data are lacking or problematic with regard to low-dose effects." The relevant published literature on this matter is either absent from the report or held to be problematic.

(1) Confounding Factors in the Southwest Taiwan Data Have Been Ignored

The issue of confounding is critically important in the assessment of the "Taiwanese dataset", presumably meaning data from the cancer study in the Blackfoot-disease endemic area of SW Taiwan published as Wu et al. (1989).[1]

The Wu et al. (1989) study population was a 42-village sub-set and expansion of the 84-village study population of Chen et al. (1985),[2] adding only the variable of village-specific median arsenic level in well water. The Chen et al. (1985) found a dose-response with respect to water source and to township; The Wu et al. (1989) only examined for (and found) a dose-response for arsenic strata level. Subsequently, Morales (2000),[3] NRC (1999, 2001),[4] and EPA (2001, 2005) have reanalyzed to data from the Wu (1989) study with village-specific median well arsenic levels (instead of arsenic strata) as the only explanatory variable.

We have published analyses of the Wu (1989) data demonstrating that the two explanatory variables that Chen (1985) had reported [water source[5] and township[6]] as significant explanatory variables of the cancer risk were also significant explanatory variables in the cancer risk analysis of Wu (1989). Village median well arsenic concentration was found to be a no-better explanation for the variability in village bladder cancer rates than was water source (artesian well dependency or exposure).[7] The inclusion of township group as a stratifying variable markedly improved the explanatory

[1] Wu MM, Kuo TL, Hwangf YH, and Chen CJ. Dose-Response Relation Between Arsenic Concentration in Well Water and Mortality from Cancers and vascular Diseases. Am J epidem, 1989;130(6):1123-1132.
[2] Chen CJ, Chuang YC, Lin TM, and Wu HY. Malignant Neoplasms among Reidents of a Blackfoot Disease-endemic Area in Taiwan: High-Arsenic Artesian Well Water and Cancers. Cancer Res, 1985 Nov;45:5895-5899.
[3] Morales KH, Ryan L, Kuo TL, Wu MM, and Chen CJ. Risk of Internal Cancers from Arsenic in Drinking Water. Env Health Persp, 2000 July;108(7):655-661.
[4] National Research Council (NRC). Arsenic in Drinking Water. National Academy of Sciences, 1999 and 2001 Update. National Academy of Sciences, Washington, DC 2001.
[5] Lamm SH, Byrd DM, Kruse MB, Feinleib M, and Lai SH. Bladder Cancer and Arsenic Exposure: Differences in the Two Populations Enrolled in A Study in Southwest Taiwan. Biom Environ Sci, 2003;16:355-368.
[6] Lamm SH. Engel A, Penn CA, Chen R, and Feinlieb M. Arsenic Cancer Risk Confounder in Southwest Taiwan Data Set. Env Health Persp, 2006 July;114(7):1077-1082.
[7] Lamm 2003. Op cit. Table 2.

power of the variable median village well arsenic level from a $R^2 = 0.21$ to $R^2 = 0.75$. Neither these papers nor their findings are cited in the Panel report.

For Blackfoot disease, for skin cancer, and for internal cancers, the literature from 1960 to 1986 focused in on high-arsenic containing artesian well water as the critical exposure factor. The Chen et al. (1985) paper labels its topic as "High-Arsenic Artesian Well water and Cancers," and the Chen et al. (1986)[8] retrospective analysis used years of artesian well water usage rather than arsenic level as the explanatory variable. The Wu et al. (1989) was developed to provide an analysis by arsenic concentration but the artesian well variable was dropped from further analysis and not included in the Morales et al. (2000)[9] paper or the analyses by NRC or EPA.

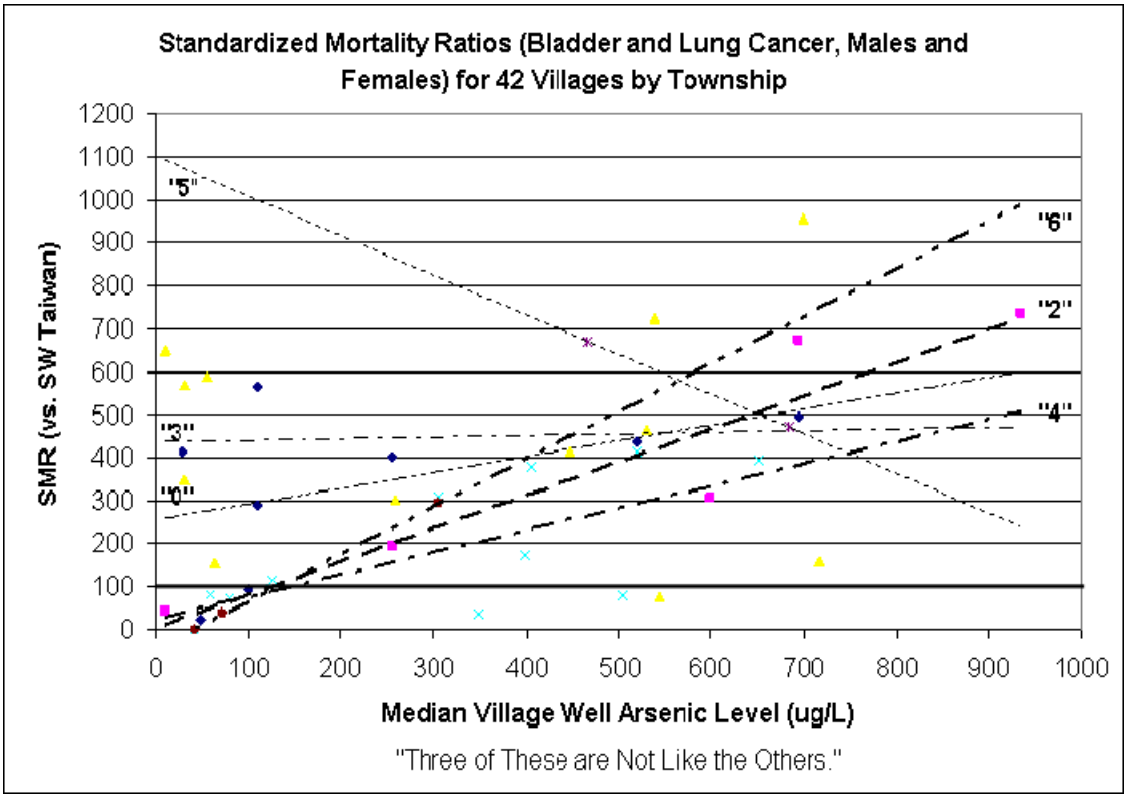
The original Southwest Taiwan internal cancer study [Chen et al., 1985] (upon which all the other Southwest Taiwan internal cancer studies are based) stated that its objective was "to elucidate the association between high-arsenic artesian well water and cancers in the endemic area of blackfoot disease." Our 2003 paper[5], using "wells with an arsenic water level of > 325 ug/L" as a surrogate identifier of artesian well waters, showed that "arsenic exposure levels do not explain bladder cancer mortality risk in SW Taiwan among villages not dependent upon artesian well water." That paper demonstrated that arsenic concentration was no better a determinant of bladder cancer risk than was water source. Additionally, a comparison[10] of the Southwest Taiwan and US 133-county study[11] data showed that "both the SW Taiwan data in the absence of high arsenic levels (< 350 ug/L) and humic acids and the U.S. 133-county data with As < 60 ug/L are consistent with no increased bladder cancer mortality with drinking water arsenic concentrations in the exposure range of observation. These analytic results are consistent with both co-carcinogenesis and high-exposure (hundreds of ug/L As) dependence models of toxicologic mode-of-action." None of the analyses that the Arsenic Review Panel depends upon has examined for water source or artesian well aquifer as an independent variable or confounder. Neither of these papers were cited in the Panel's report.

With respect to the Southwest Taiwan dataset, Lamm et al. (2006)[7] recognized that the SW Taiwan dataset has been pooled from six townships and examined whether the arsenic-cancer dose-response relationship (bladder and lung cancer combined) was similar across the townships. It found that it was not. This methodology is similar to that of examining for heterogeneity across plants in an occupational study or across study sites in a multi-center clinical study. This paper showed that a second carcinogenic factor, demonstrated as township, confounded the risk analysis. Stratification by

[8] Chen CJ and Wang CJ. Ecological Correlation between Arsenic Level in well Water and Age-adjusted Mortality from Malignant Neoplasms. Cancer Res, 1990 sept 1;50:5470-5474.
[9] Lamm SH and Kruse MB. Arsenic Ingestion and Bladder Cancer Mortality – What Do the Dose-Response Relationships Suggest About Mechanism? Human Ecol Risk Ass, 2005 Apr;11(2):433-450.
[10] Lamm SH and Kruse MB. Arsenic Ingestion and Bladder Cancer Mortality – What Do the Dose-Response Relationships Suggest About Mechanism? Human Ecol Risk Ass, 2005 Apr;11(2):433-450.
[11] Lamm SH, Engel A, Kruse MB, Feinleib M, Byrd DM, Lai S, and Wilson R. Arsenic in Drinking Water and Bladder Cancer Mortality in the United States: An Analysis Based on 133 U.S. Counties and 30 Years of Observation. 2004; 46:298-306.

township revealed that three townships (Townships 0, 3, and 5) exhibited a significant background cancer risk that was independent of arsenic exposure and that three townships (Townships 2, 4, and 6) exhibited a significant dose-response curve with arsenic exposure that showed similar thresholds (i.e., inflection point or no prior risk point). This paper reported that "the data for bladder and lung cancer mortality for townships 2, 4, and 6 fit an inverse linear regression model ($p < 0.001$) with an estimated threshold at 151 ug/L (95% confidence interval, 42 to 229 ug/L)." This work has been presented to the Panel but was neither cited nor apparently considered.

Three townships show a significant cancer risk that is independent of arsenic exposure, and three townships each show a similar significant arsenic-cancer dose-response that is highly dependent on arsenic level. Further, this dependency does not fit a model through the origin but does fit a "non-linear" model with increased cancer risk above 151 ug/L (95% confidence interval, 42 to 229 ug/L) arsenic in the drinking water.



The term "non-linear" model is a misnomer. The contrast is between a linear model through zero as the x-intercept and a linear model with a non-zero x-intercept. The data do fit a linear model, but a linear model with an x-intercept significantly greater than zero.

Some of what the Panel reports from Taiwan is not from SW Taiwan. The Panel report identifies the Chen et al. (2004)[12] lung cancer study as a follow-up of the Taiwanese cohort with "limited power to examine the form of the dose-response relationship within the 10-100 ug/L range." The study is a report on the pooled data of three cohorts, two in the Blackfoot disease area and one in the NE non-Blackfoot disease area, in which only 2 % of those in the 10-199 ug/L were recruited from SW Taiwan as were 18% of the reference population. While a significant dose-response is presented for exposures of 100 ug/l or greater arsenic, this is not interpretable without disaggregating the study populations.

No attention is given to the issue of selection bias in the SW Taiwan dataset. All the Southwest Taiwan data come from 42 of the 115 villages in the Blackfoot disease endemic area but the reasons that these villages in particular had well arsenic levels is not known. Later, Chen et al. (1996)[13] reported on 60 villages. Furthermore, more than half the Wu (1989) villages in the study had only a single exposure data point. The selection factors for determining which village wells had arsenic measurements made and why are unknown. The number of samples for each well are unknown, and it is presumed that every well in each village was included.

(2) The US 133-County Study Has Been Inadequately and Improperly Considered

The Arsenic Research Panel (page 49) has determined that the US 133-county study (Lamm et al., 2004),[14] should be given little weight because its exposure assessment is "highly problematic" and based on median county-level exposure values for which "it is not clear that these are the arsenic exposure values for large numbers of residents within each county." This is an incomplete description and an ungrounded speculation.

Unlike the SW Taiwan study data analyses, the 133-county study presented parallel analyses using both the median and the mean concentrations. These analyses, presented graphically (Figures 2 and 3) and in weighted regressions (Table 2), all showed similar slopes that were indistinguishable from zero. The slope estimates ranged from -5.1E-6 to +6.7E-6 and did not extend as high as the NRC 2001 predicted slope of +4.5E-5.

[12] Chen CL, Hsu LI, Chiou HY, Hsueh YM, Chen SY, Wu MM, and Chen CJ. Ingested Arsenic, Cigarette Smoking, and Lung Cancer Risk – A Follow Up Study in Arseniasis-endemic Areas in Taiwan. JAMA, Dec 22/29, 2004; 292(24):2984-2990.

[13] Chen CJ, Chiou HY, Chiang MH, Lin LJ, and Tai TY. Dose-Response Relationship Between Ischeic Heart Disease Mortality and Long-Term Arsenic Exposure. Arteriosclerosis, Thrombosis, and Vascular Biology, 1996 april;16(4):504-510.

[14] Lamm SH, Engel A, Kruse MB, Feinleib M, Byrd DM, Lai S, and Wilson R. Arsenic in Drinking Water and Bladder Cancer Mortality in the United States: An Analysis Based on 133 U.S. Counties and 30 Years of Observation. 2004; 46:298-306.

There is no basis to speculate that large numbers of residents were not exposed to the groundwater arsenic levels. The use of any central tendency of an exposure spectrum may not reliably represent persons at the far end of the spectrum, but there is no reason to believe that these would be large numbers of residents and the populations would be consistently biased to the right of the median across 133 counties. In the selection process for the counties, we were specifically informed by the state departments of environmental protection that the county's drinking water supply was entirely supplied by ground water both currently and historically, i.e., that there was no surface water supply. Thus, the ground water arsenic levels should be a reasonably reliable estimation of the exposure of the residents within each county. In other studies, the use of bottled water may be a significant alternative source of drinking water; however, in this study the periods of observation (1950-1979) and of exposure (1900-1979) were earlier than the recent era of popular bottled water consumption.

The 133-county US study was designed to be a US replicate of the SW Taiwan study. It uses data aggregated at the county level, while the SW Taiwan study uses data aggregated at the village level. It has a 30-year observation period, while the SW Taiwan has a 14 year observation period. Both studies use a median arsenic exposure with the US based on USGS data. Neither study has individual well use histories as is found in the Inner Mongolia study.[15] The underlying data for the US study are available through the USGS; the data underlying the NRC A-10 table are not available.

Each has issues on migration. Local inter-county migration in the US may have less impact on county-based arsenic exposure because of the large size of aquifers; Local inter-village migration in SW Taiwan should have more impact on village-based arsenic exposure because of the geographically patchy variation in village arsenic levels in the Blackfoot disease area (See attached map from Wu et al., 1989) and the matrilocal vs. patrilocal migrations with marriage.

The two studies presumably have similar degrees of cancer ascertainment. The US study includes 4,537 male bladder cancer deaths; The SW Taiwan study has 85. The US study shows a flat curve until 60 ug/L;[16] The SW Taiwan data shows a flat curve until 400 ug/L for bladder mortality.[17]

The Panel has been concerned that the bladder cancer mortality pattern observed in the 133-county US study is problematic because the county median arsenic levels may not be fully representative of the exposed populations. Additional evidence supporting the observation of no increased cancer risk at low levels of exposure to inorganic arsenic is provided by another US multi-county cancer mortality study with a different and well-characterized arsenic exposure assessment, one that uses a population-weighted mean arsenic level.

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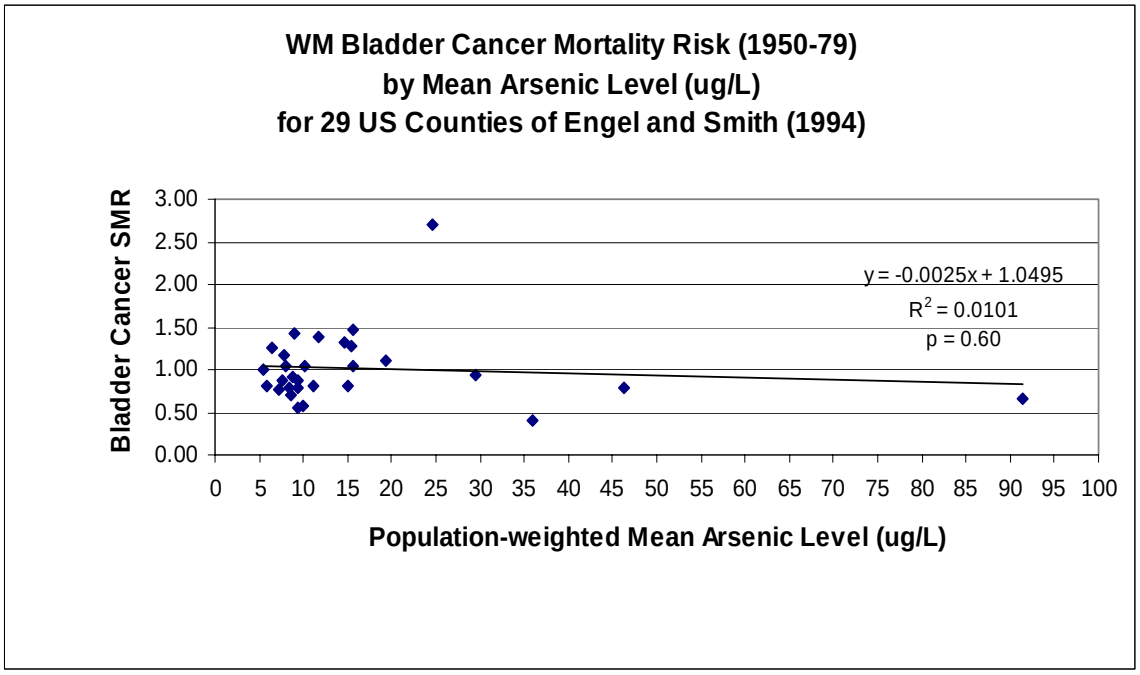
[15] Tucker SB, Lamm SH, Li FX, Wilson R, Byrd DM, Lai S, Tong Y and Loo L. Relationship between consumption of Arsenic-Contaminated well Water and Skin Disorders in Huhhot, Inner Mongolia. Agency for Toxic Substance and Disease Registry (July 5, 2001).
[16] Lamm (2004). Op Cit Table 1.
[17] Morales (2000). Op cit. Table 5.

In 1994, Engel and Smith[18] published a study based on data obtained on arsenic in public water systems for all 50 US states, the District of Columbia, and Puerto Rico. They calculated population-weighted mean arsenic levels for each county and identified the 30 counties with population-weighted mean arsenic levels greater than 5 ug/L (range: 5.4-91.5 ug/L). Their particular focus was on vascular diseases but did include some cancer mortality data. We have sought the white male bladder cancer mortality data[19] for these 30 counties, found it for 29 counties, and demonstrate them graphically below.



Thus, the speculation that the non-positive dose-response seen in the US 133-county study is due to missing large groups of residents with exposure quite different from the median is not supported. The dose-response pattern for the WM bladder cancer mortality by county based on the Engel and Smith (1994) arsenic exposure ascertainment appears to be the same as, or similar to, the dose-response pattern based on the Lamm et al. (2004) arsenic exposure ascertainment. We see this as an external validation of the exposure assessment presented in our 2004 paper.

(3) The Report Fails To Adequately Consider Low-Dose Exposure Studies

[18] Engel RR and Smith AH. Arsenic in Drinking Water and Mortality from Vascular Disease: An Ecological Analysis in 30 Counties in the United States. Arch Env Health, Sept/Oct 1994; 49(5):418-427.
[19] United States Environmental Protection Agency and National Cancer Institute. *U.S. Cancer Mortality Rates and Trends, vol II, 1950-1979*; 1984.

The Panel rejected the three low-dose exposure bladder cancer studies (Lamm et al., 2004; Bates et al. 2003[sic][20]; and Steinmaus et al. 2003[21]) as "lacking statistical power and (having) estimations of low dose risk [that] tend to be unstable and to have a high degree of uncertainty." The Panel concluded that "There is no human data available that is adequate to characterize the shape of the dose-response curve below a given point of departure."

Each of these studies showed a flat dose-response curve in the low dose range. The US 133-county bladder cancer study presented a dose-response analysis across seven strata in the 3-60 ug/L range and concluded that "No arsenic-related increase in bladder cancer mortality was found over the exposure range of 3 to 60 ug/L using stratified analysis and regression analysis (both unweighted and weighted by county population and using both mean and median arsenic concentrations)." Similarly, the Bates (2004) study reported that their "study found no association between estimated arsenic exposures (> 80 ug/day) and bladder cancer risk … and even a suggestion of a risk reduction at high arsenic levels (page 387)." Likewise, the Steinmaus (2003) study reported "no increased risks were identified for arsenic intakes greater than 80 ug/day (OR = 0.94, 95% CI, 0.56-1.57; p (linear trend) = 0.48) [and that] these risks are below predictions based on high dose studies from Taiwan (abstract)." The Panel has not informed the reader on any of these results.

The findings of each of the three studies of bladder cancer risk for low-dose arsenic exposure populations that the Panel considered to be problematic showed a non-negative slope. It is not my proposal to attempt to do a pooling analysis to determine whether as a set the studies demonstrate a significant negative slope, rather it is my perception that confounding exposures explain a sizable proportion of the variability at low dose levels.

A pooling, or meta-analysis, however, was presented to the Panel by Mink et al. (2006).[22] They found across the bladder cancer literature no arsenic-attributable bladder cancer risk for non-smokers and a confounded risk pattern for smokers. That analysis concluded that "exposure to arsenic at low levels is not an independent risk factor for bladder cancer and found that the data indicate a non-linear association between arsenic in drinking water and bladder cancer, with a likely threshold dose between 100-250 ug/L." A recent study[23] of male smokers in Finland reported that "our results suggest that arsenic exposure levels of about 50 ug/liter do not increase the risk of bladder

[20] Bates MN, Rey OA, Biggs ML, Hopenhayrn C, Moore LE, Kalman D, Steinmaus C, and Smith AH. Case-Control Study of Bladder Cancer and Exposure to Arsenic in Argentina. Am J Epidem, 2004; 159:381-389.

[21] Steinmaus C, Yuan Y, Bates MN, and Smith AH. Case-Control Study of Bladder Cancer and Drinking Water Arsenic in the Western United States. Am J Epidem, 2003; 158:1193-1201.

[22] Mink PJ, Alexander DD, Barraj LM, Kelsh MA, and Tsuji JS. Epidemiologic Studies of Low-Level Arsenic Exposure in Drinking Water and Bladder Cancer – A Review and Meta-Analysis. Arsenic Research Panel meeting, September 2005.

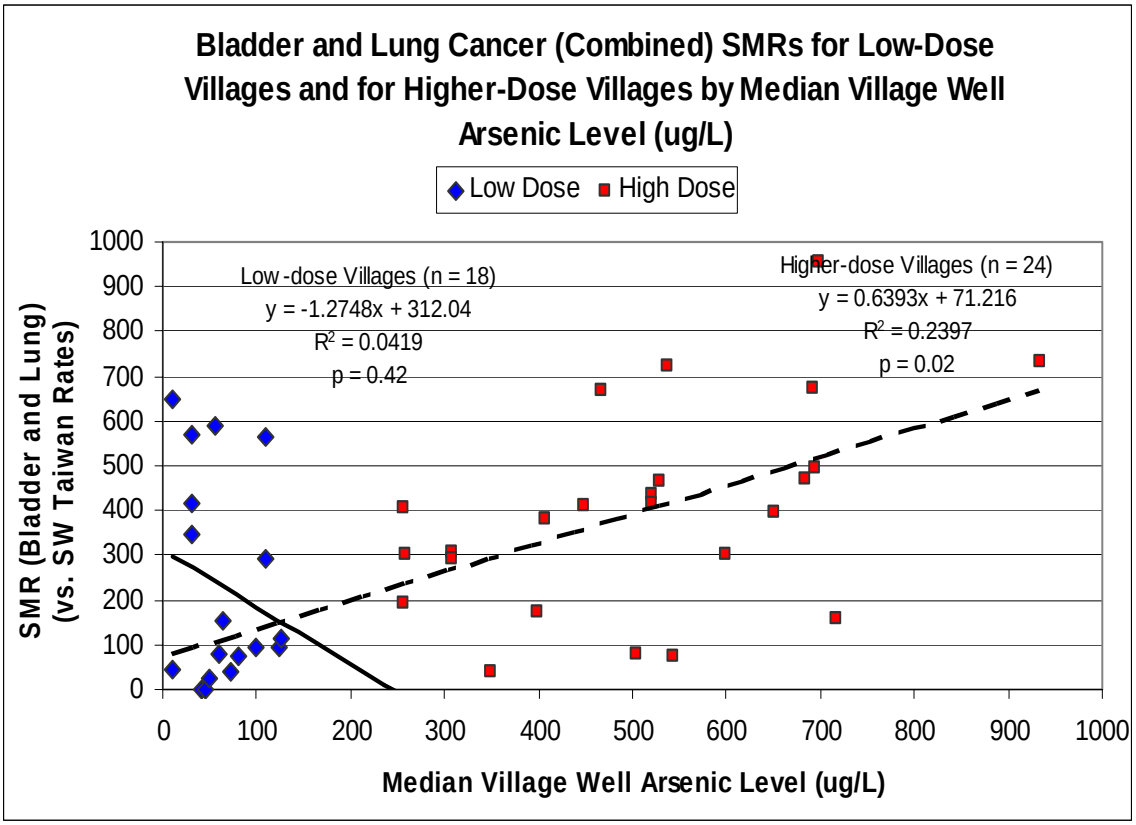
[23] Michaud DS, Wright ME, Cantor KP, Taylor PR, Virtano J, and Albanes D. Arsenic Concentrations in Prediagnostic Toenails and the Risk of Bladder Cancer in a Cohort Study oif Male Smokers. Am J Epid, 2003 Sept;160(9):853-859.

cancer…(though they) could not exclude the possibility that exposure levels of about 100 ug/liter may be associated with bladder cancer."

The Panel seems to desire that data demonstrate a "dose-response curve below a given point of departure" in order to be able epidemiologically to confirm the threshold model that has been demonstrated toxicologically. This is faulty logic. The threshold (non-linear) model predicts that below the inflection point there will be no dose-response curve (i.e., the data will not demonstrate a statistically significant positive slope).

The EPA asked the Panel whether the "Taiwanese dataset remains the most appropriate choice for estimating cancer risk in humans?" However, the Panel restricted its response by assuming that only a non-threshold model (i.e., a cancer unit risk model) could be used to estimate cancer risk in humans. The Panel determined (page 40) that "the Taiwanese database remains the most appropriate choice for deriving the cancer unit risk" as if the risk at high-dose exposure predicted the risk at low-dose exposure.

However, even in the Taiwan dataset, it is clear that the risk at high-dose exposure has not predicted the risk at low-dose. Further, the data for the low-dose villages themselves show a non-significant negative slope (see below). Further, even visually the low-dose data suggest some confounding with somewhat more than half the villages having an SMR 100 (range zero-200) and the rest having an SMR of 300-650. We presented (September 12, 2005) to the Panel an analysis of the low-dose village cancer mortality showing that the strongest significant determinant was township and that median arsenic level was not a significant determinant (as apparent in the figure below).



In summary, the Panel has stated (page 36) that "if epidemiological data could be strengthened at the low-dose range to demonstrate either a low-dose benefit or no effect at low dose, then a threshold is certain." However, the Panel has either rejected the relevant articles as being problematic or has not cited them.

The draft letter to the EPA Administrator states that "the dose response for human data in the low dose region does not describe clearly the shape of the curve, but they do fit with a linear model." With respect to the Southwest Taiwan data, this statement is in error. Based on the data from the townships that demonstrate an arsenic-cancer dose response, the dose response for human data in the low and high dose regions do describe clearly the shape of the curve, and together they do not fit a linear model.

In essence, the SAB has been asked by EPA to determine whether the EPA can continue to rely on analyses of the Morales et al. (2000) database from the Wu et al. (1989) study for assessing the dose-response relationship for arsenic ingestion and internal cancers.

Identification of confounding within the Southwest Taiwan dataset which has developed over the past five years makes the prior analyses invalid. Proper evaluation of that dataset and proper consideration of the many pertinent low-dose studies support an overall non-linear (i.e., threshold) model for human cancer risk from the ingestion of inorganic arsenic.

Respectfully submitted,

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Attachments:

1. Lamm et al. (2004). US 133-county study.
2. Lamm et al. (2006). Township analysis of SW Taiwan study.
3. Wu et al. (1989) map.